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**The effect of individualized analgesia
on respiratory adverse events after
adenotonsillectomy in Children
—randomized double-blind controlled trial**

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Study protocol

Study background

Adenotonsillectomy in children is a common operation in Department of ENT, and it is also the main method for treatment of obstructive sleep apnea syndrome (OSAS). Clinically, there are a considerable number of children with OSAS who underwent adenotonsillectomy, some of which are severe OSAS.

Recurrent nocturnal hypoxemia occurred in children with severe OSAS. Their susceptibility to opioids increased and the quantity of opioid needed for no pain after operation was less than that of mild children . Therefore, the dosage of opioids for postoperative analgesia in children with different severity is different. If all children are treated with a small dose of opioid analgesics, the analgesic efficacy of mild or non OSAS children is not sufficient; if a large dose is used, then severe children are prone to respiratory adverse events . Studies have shown that the incidence of respiratory adverse events in children with severe OSAS is as high as 29.6%, which is about 10 times that of children with mild OSAS. Therefore, it is very important to differentiate the patients with severe and mild OSAS for targeted individualized use of analgesics in children with adenotonsillectomy .

Since children with severe OSAS have an increased susceptibility to opioids, we hypothesized that the sensitivity of children to opioids could

be judged by the response of respiratory rate to small doses of opioids, which can guide the use of long-acting opioids after surgery to reduce the incidence of respiratory adverse events. Based on our previous studies, we found that the fentanyl test results were correlated with the postoperative morphine requirement. Children with positive fentanyl test need less morphine requirement (median morphine use was 30µg/kg), and negative children need less postoperative morphine requirement (median morphine use was 50µg/kg) . It shows that the conventional analgesic dose (25 µg/kg) is larger for some of the children with positive fentanyl, which may increase the incidence of postoperative respiratory adverse events . It is small for the children with negative fentanyl test, there is a lack of pain relief, which extends the duration of pain in children. Fentanyl test cannot identify the severity of OSAS, but it can be used to identify children with different morphine requirements. Therefore, we hypothesized that individual analgesia should be performed according to the results of fentanyl test. More amount of morphine in children with positive fentanyl test and less amount of morphine in children with negative fentanyl test can reduce the incidence of postoperative adverse events in children ,and improve the analgesic efficacy of children.

Objective

The aim of this study was to verify the hypothesis that individualized

opioid analgesia regimen according to fentanyl test could decrease the incidence of postoperative respiratory adverse events and improve the effect of analgesia compared with conventional opioid analgesia regimen after adenotonsillectomy in children.

Materials and Methods

The study received approval from the Institutional Review Board of the Children's Hospital Fudan university (Human Research Review Committee Approval No.2016189) and written parental informed consent. In this prospective, double-blind, randomized, controlled clinical trial, 280 children scheduled for adenotonsillectomy under general anesthesia at the Children's Hospital from November 2016 through February 2017 were selected and were randomly divided into two groups. One group was conventional opioid analgesia regimen group, another was individualized opioid analgesia regimen group. The two groups had the same anesthesia regimen. Intubation was performed without muscle relaxants after induction with inhaled sevoflurane combined with propofol. Anesthesia was maintained with sevoflurane and N₂O without opioids during the operation. Before extubation, spontaneous respiration was recovered, and respiratory rate were monitored after administration of 1μg/kg fentanyl intravenously. A positive result was defined as a decrease of more than 50% in spontaneous respiratory rate. Otherwise it was defined as a negative

result. Extubation was performed when patients were fully awake, and they were transferred to the post-anesthesia care unit (PACU). Pain was evaluated based on the Children's Hospital of Eastern Ontario Pain Score (CHEOPS) upon admission into the PACU, and every 10 minutes thereafter. Morphine was administered repeatedly every 10 minutes until a CHEOPS of 6 was attained. Patients in the individualized group with positive results of fentanyl test received morphine 10µg/kg intravenously, while patients with negative results received morphine 50µg/kg intravenously. In the conventional group all patients received 25µg/kg morphine. The main observation indexes was the incidence of respiratory adverse events in PACU, the ratio was the number of children who occurred respiratory adverse events to the total number of children. Respiratory adverse events were defined as an intervention requiring a nurse to maintain the SPO₂ ≥95%. Interventions include blow-by-oxygen mask, jaw thrust, change the body position, pressure ventilation, the need to establish artificial airway (oropharyngeal or nasopharyngeal airway, laryngeal mask, the endotracheal tube), drug administration (succinylcholine or propofol ease laryngospasm, salbutamol inhalation ease bronchospasm, etc.). Secondary indexes were the pain score of children in two groups, and analyzed the persistent pain state of children in the two groups by Kaplan-Meier survival analysis.

Statistical Analysis

the SPSS 23.0 (Statistical Package for Social Sciences, IBM) was used to analyze the data. The measurement data are tested by normality, and the normal distribution is expressed as the mean \pm standard deviation; if the distribution is not normal, it is represented by the median and range interquartile. The measurement data with normal distribution and homogeneity of variance uses t test, if heterogeneity of variance, use the nonparametric test; Chi square test was used to compare the count data.

Results

The rate of postoperative respiratory adverse events were the main observation indexes, comparative the differences, RR (relative risk) and the NNT (number need to treat). We also compare the median survival time of CHEOPS > 6 in the individualized group and conventional group. At 20 minutes in the PACU, the proportion of children who reached a score of CHEOPS \leq 6 in the individualized group and conventional group. $p < 0.05$ was considered statistically significant.

Summary

There are few studies on how to guide the opioid analgesic dosage in children with OSAS according to their sensitivity to opioids. In our study, the individualized analgesic regimen guided by fentanyl test may reduce the incidence of respiratory adverse events after adenotonsillectomy and improve the postoperative safety of children.